Patents

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#28 M.M. 10/2/03

In re Application of:	)	
	)	
AGOSTON ET AL.	)	
	)	Art Unit: **1616**
Serial No.: **09/644,387**	)	
	)	Examiner: **Badio, B.**
Filed: **August 23, 2000**	)	
	)	
For: **METHODS OF OBTAINING 2-METHOXYESTRADIOL OF HIGH PURITY**	)	

APPELLANT'S APPEAL BRIEF

Commissioner of Patents & Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

To the Honorable Board of Patent Appeals and Interferences:

1. Real Party In Interest

The present application is assigned to EntreMed, Inc., 9640 Medical Center Drive, Rockville, MD 20850.

2. Related Appeals and Interferences

Appellant is not aware of any related appeals or interferences.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on **September 19, 2003.**

Robert E. Richards, Reg. No. 29,105

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3. Status of Claims

On August 14, 2003, Appellant appealed from the final rejections of Claims 1-13 and 21-25. No claims have been allowed in this application.

4. Status of Amendments

No amendments were submitted subsequent to final rejection.

5. Summary of the Invention

Appellants' invention is drawn to a pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 99.5% as determined by HPLC (Claim 1). Ultra-low levels of typical synthesis impurities, such as estradiol and estrone, are claimed (Claims 2, 3 and 7). Claim 8-10 are drawn to a pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 98.0% containing less than 0.03% estradiol and less than 0.02% estrone, while Claims 21-25 are directed to pharmaceutical compositions being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 98.0% and ultra-low levels of typical synthesis impurities, such as estradiol and estrone. Claims 21-25 also recite the process by which those pharmaceutical compositions are produced. Claims 11-13 are directed to pharmaceutical compositions being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 99.0% and ultra-low levels of typical synthesis impurities, such as estradiol and estrone. Reduced levels of synthesis intermediates, such as 2-hydroxyestradiol, 4-hydroxyestradiol and 4-methoxyestradiol, are also addressed in the claims.

6. **Issues:**

(1) Are Claims 1-13 and 21-25 unpatentable under 35 U.S.C. § 103 as being obvious over U.S. Patent No. 5,504,074 to D'Amato et al., U.S. Patent No. 5,521,168 to Clark, U.S. Patent No. 5,643,900 to Fotsis et al., or U.S. Patent No. 6,200,966 to Stewart et al.

Claims 1-13 and 21-25 were rejected under 35 U.S.C. § 103(a) as being obvious and unpatentable over the patents to D'Amato et al., Clark, Fotsis et al. and Stewart et al. The Examiner asserts that utilizing a pure form of any pharmaceutical agent in the medical art would be obvious to the skilled artisan because of the desire to reduce any adverse effects caused by contaminants. The Examiner further states that obtaining a pure form of a steroid compound free of any contaminant, including other steroids, would be obvious to the skilled artisan because the skilled artisan would recognize that the terms "impurities" and "contaminants" are inclusive, and, thus, refer to that which is not desired.

Appellants are claiming pharmaceutical composition comprising 2-methoxyestradiol that contains extremely low levels of synthesis impurities not disclosed or suggested in the prior art. The Examiner's position is basically that it is obvious to make a pure pharmaceutical composition. Appellants contend that the Examiner has failed to consider the teaching of the prior art as a whole

Appellants further contend that the term "pure," as used by the Examiner, is a relatively term. For one application, a purity of 95% may be sufficient; whereas, for another application a purity of 98% may be sufficient. What purity is sufficient depends on the application for which the drug is intended and the nature of the "contaminants" or "impurities." For example, a drug for treating humans may comprise 75% of an active ingredient and 25% of an innocuous impurity. The drug is only 75% pure, but the other 25% is not harmful to humans. On the other hand, a drug for treating humans may comprise 98.5% of an active ingredient and 0.5% of a toxin. Although the drug would appear on its face to be "pure" at 98.5%, it is potentially dangerous because of the 0.5% toxin. Therefore, focusing only on the "purity" of a drug can be misleading. One must look past the superficial purity of a pharmaceutical composition and examine the amounts and types of the "impurities" or "contaminants."

Furthermore, in order to appreciate whether a component of a pharmaceutical composition is an "impurity" or a "contaminant," there must be an appreciation in the art that such a component is undesirable for the application for which the drug is to be used.

It is this last element that is completely missing in the present case. Not only is there a lack of appreciation in the art that certain components are not desirable for a drug comprising 2-methoxyestradiol, the art identifies those certain components as useful or desirable. The art therefore does not view these components as "impurities" or "contaminants," but, rather, as components having the same activity as the active ingredient. In this sense there is a teaching away from the present invention. And, since the art, as a whole, does not view these components as "impurities" or "contaminants," it would not be obvious to a person skilled in the art, at the time the invention was made, to remove those components to the levels presently claimed.

The present invention claims a pharmaceutical composition comprising 2-methoxyestradiol. It is well known in the art that in order to make 2-methoxyestradiol, one starts with estradiol or estrone. Thus, estradiol and estrone are typical impurities comprising unreacted starting materials. In the process of substituting the "A" steroidal ring at the 2-position, some substitution at the 4-position inevitably occurs. Therefore, 2-hydroxyestradiol and 4-hydroxyestradiol are typical intermediates in the manufacturing process. Conversion of the 2-hydroxy substituent to the desired 2-methoxy substituent also converts any 4-hydroxyestradiol to 4-methoxyestradiol. Therefore, 4-methoxyestradiol is also a typical impurity. Thus, it is inherent in the manufacturing process of 2-methoxyestradiol that estradiol, estrone, 2-hydroxyestradiol, 4-hydroxyestradiol and 4-methoxyestradiol are present.

Due to a total lack of appreciation in the art, and particularly in the prior art cited in the present application, that estradiol and estrone are undesirable components in a pharmaceutical composition comprising 2-methoxyestradiol, the claimed ultra-low levels of estradiol and estrone in the present pharmaceutical composition is nonobvious. Similarly, due to a total lack of appreciation in the art, and particularly in the prior art cited in the present application, that 2-hydroxyestradiol, 4-hydroxyestradiol and 4-methoxyestradiol are undesirable component in a pharmaceutical composition comprising 2-methoxyestradiol, the claimed ultra-

low levels of 2-hydroxyestradiol, 4-hydroxyestradiol and 4-methoxyestradiol in the present pharmaceutical composition is nonobvious.

7. Grouping of Claims

For the reasons stated below, the Appellants contend that not all of the rejected claims stand or fall together, but the following groups are each separately patentable in view of the art relied upon by the Examiner.

Groupings	Rejection Under § 103(a) Over D'Amato et al., Clark, Fotsis et al. or Stewart et al.
Group I	Claim 1
Group II	Claims 2, 3 and 7
Group III	Claims 4-6
Group IV	Claims 8-10 and 21-25
Group V	Claims 11-13

8. Argument

A. Introduction

As stated above, the key to determining whether a composition is sufficiently "pure" is determining the nature of the "impurity." If a component is not recognized by the art, as a whole, as undesirable, there can be no appreciation that the component is an "impurity." If a component is not recognized as an "impurity," there would be no motivation from the art to remove it. Thus, it would not be obvious to a person skilled in the art to remove or reduce the amount of that component to the levels presently claimed in order to make a "pure" pharmaceutical composition.

The error committed by the Examiner in making the final rejection on appeal was not considering the lack of appreciation of the art that estradiol and estrone are undesirable components in a pharmaceutical composition comprising 2-methoxyestradiol. The Examiner also erred in making the final rejection by not considering the lack of appreciation of the art that 2-hydroxyestradiol, 4-hydroxyestradiol and 4-methoxyestradiol are undesirable components in a pharmaceutical composition comprising 2-methoxyestradiol.

As stated above, estradiol, estrone, 2-hydroxyestradiol, 4-hydroxyestradiol and 4-methoxyestradiol are inherently present in 2-methoxyestradiol due to the synthesis process for making 2-methoxyestradiol. Whether or not any one or more of those components should be removed from 2-methoxyestradiol and the level to which they are to be removed depends entirely on whether the prior art views each of those compounds as undesirable for a 2-methoxyestradiol pharmaceutical composition.

Appellants submit that in the present application, not only does the prior art of record not provide any motivation to remove one or more of the foregoing components, the prior art teaches away from the removal of one or more of those components.

The claims presently under rejection contain various combinations of reduced levels of the unreacted starting materials; *i.e.*, estradiol and estrone, and reduced levels of synthesis intermediates; *i.e.*, 2-hydroxyestradiol, 4-hydroxyestradiol and 4-methoxyestradiol. The claims also include different overall measurements of the purity of the pharmaceutical composition. These various combinations are shown below for the five different grouping of claims.

Group I – Claim 1:

Appellants' invention is drawn to a pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 99.5% as determined by HPLC (Claim 1).

Group II- Claims 2, 3 and 7:

Appellants' invention is drawn to a pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 99.5% as determined by HPLC. Claim 2 further provides that the composition contains less than 0.03% estradiol and less than 0.02% estrone. Claim 3 further provides that the composition contains less than 0.01% estradiol and less than 0.01% estrone. Claims 7 further provides that the composition contains 0.01% or less estradiol, 0.01% or less estrone, 0.02% or less 2-hydroxyestradiol, 0.01% or less 4-hydroxyestradiol, 0.01% or less 4-methoxyestradiol.

Group III – Claims 4 through 6:

Appellants' invention is drawn to a pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 99.5% as determined by HPLC. Claim 4 further provides that the composition contains less than 0.02% 2-hydroxyestradiol. Claims 5 further provides that the composition contains less than 0.02% 4-hydroxyestradiol. Claim 6 further provides that the composition contains less than 0.02% 4-methoxyestradiol.

Group IV – Claims 8-10 and 21-25:

Appellants' invention is drawn to a pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 98.0% and containing less than 0.03% estradiol

and less than 0.02% estrone (Claims 8 and 21-25). Claim 9 further provides that the composition contains less than 0.01% estradiol and less than 0.01% estrone. Claim 10 further provides that the composition contains 0.01% or less estradiol, 0.02% or less 2-hydroxyestradiol, 0.01% or less 4-hydroxyestradiol, 0.01% or less 4-methoxyestradiol and 0.01% or less estrone.

Group V – Claims 11-13:

Appellants' invention is drawn to a pharmaceutical composition being substantially free of steroid contaminants having estrogenic or carcinogenic effects comprising 2-methoxyestradiol having a purity greater than 99.0% and containing less than 0.03% estradiol and less than 0.02% estrone (Claim 11). Claim 12 further provides that the composition contains less than 0.01% estradiol and less than 0.01% estrone. Claim 13 further provides the composition contains 0.01% or less estradiol, 0.02% or less 2-hydroxyestradiol, 0.01% or less 4-hydroxyestradiol, 0.01% or less 4-methoxyestradiol and 0.01% or less estrone.

Group I is separately patentable from the other groups because it is not specific with respect to the ultra-low levels of impurities that are permitted in the pharmaceutical composition. Instead, Group I states that the pharmaceutical composition is substantially free of steroid contaminants having estrogenic or carcinogenic effects and is 99.5% pure as measured by HPLC. The prior art does not disclose or suggest a pharmaceutical composition of 2-methoxyestradiol of this purity. Groups II through V are separately patentable because they specify various combinations and various ultra-low levels of impurities, such as estradiol, estrone, 2-hydroxyestradiol, 4-hydroxyestradiol, and 4-methoxyestradiol. The prior art does not disclose or suggest a pharmaceutical composition of 2-methoxyestradiol having these ultra-low levels of estradiol and estrone. Furthermore, the prior art does not disclose or suggest a pharmaceutical composition of 2-methoxyestradiol having these ultra-low levels of 2-hydroxyestradiol, 4-hydroxyestradiol, and 4-methoxyestradiol.

B. The Cited Art Does Not Recognize the Problem

Appellants' written description (page 2, lines 16-27) specifically recognizes the problem of steroid impurities, such as estradiol, estrone, 2-hydroxyestradiol, 4-hydroxyestradiol, 4-methoxyestradiol, and other estrogenic metabolites, which exhibit estrogenic or carcinogenic effects that counteract the therapeutic effects of 2-methoxyestradiol. D'Amato et al., Clark, Fotsis et al., and Stewart et al. all fail to recognize this problem. To establish a *prima facie* case of obviousness where the advance lies in the discovery of the problem or the source of the problem, the Examiner would have to provide evidence that a person of ordinary skill in the art at the time of the invention would have expected a problem to exist. *In re Peehs*, 612 F.2d 1287, 204 U.S.P.Q. 835 (CCPA 1980). The Examiner has provided no such evidence, and in fact has *cited art that demonstrates the utility of the very steroid impurities the Appellants seek to remove.*

Appellants have discovered that the purity of a pharmaceutical composition is critical, as the composition comprising 2-methoxyestradiol must be substantially free of steroid contaminants having estrogenic or carcinogenic effects. Appellants respectfully maintain that the present rejection can only be made with hindsight, using knowledge of Appellants' disclosure. Hindsight is impermissible and only facts gleaned from the cited references themselves may be used in making this determination (MPEP § 2142). As a result, knowledge of Appellants' disclosure must be put aside in making a determination of obviousness (MPEP § 2142). In the present case, the Examiner has failed to follow this principal of law, and, thus, has erred in making the final rejection on appeal.

Ex Parte Morozumi et al., 1998 WL 1674768 (Bd. Pat. App. & Interf.) (copy attached hereto) is instructive in the present case. In *Ex Parte Morozumi et al.*, the appellant claimed solid 2-octynyl adenosine having a water content of not more than 3%. The examiner

had rejected the claims in view of prior art references disclosing 2-octynyl adenosine. In reversing the examiner's rejection of the claims, the Board stated as follows:

> Second, whether or not applicants solved "a very simple problem" (citation omitted) "is not inimical to patentability." (Citations omitted).
>
> Third, In re Sponnoble, 405 F.2d 578, 160 USPQ 237 (CCPA 1969), teaches at 585, 160 USPQ at 243:
>
> > ...[A] patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified. This is part of the "subject matter as a whole" which should always be considered in determining the obviousness of an invention under 35 U.S.C. § 103.
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> ***
>
> We certainly agree that it would have been well within the ordinary skill of the artisan to optimize a result effective variable. In re Boeschm 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980). Moreover, we see no clear error in the examiner's finding that purity is considered a result effective variable for most drugs. However, we do not see that persons skilled in the art would have necessarily considered water of hydration to be an impurity. To the contrary, persons having ordinary skill in the art reasonably would have been justified in presuming that Miyasaka and Matsuda had purified their 2-octynyl adenosine sufficiently for effective use as an antihypertensive agent and optimum pharmaceutical activity.
>
> ***
>
> In re Dow Chemical Co., 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988), teaches at 472, 5 USPQ2d 1531:
>
> > The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art.... Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure.

As stated above, neither the suggestion nor the expectation of success are found in the references relied upon by the Examiner. In fact the opposite is true. The suggestion of the prior art in the present case is that estrogenic metabolites, such as estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 4-methoxyestradiol, and estrone, are useful components. There is no

suggestion whatsoever that any of estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 4-methoxyestradiol, and estrone are deleterious and should be viewed as impurities or contaminants in a 2-methoxyestradiol pharmaceutical composition. Therefore, the prior art relied upon by the Examiner is devoid of any suggestion to remove any one of estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 4-methoxyestradiol, or estrone from a 2-methoxyestradiol pharmaceutical composition.

In view of the holding in *Ex Parte Morozumi et al.*, Appellants respectfully maintain that Claims 1-13 and 21-25 are not rendered obvious by D'Amato et al., Clark, Fotsis et al., or Stewart et al. under 35 U.S.C. § 103(a) for the foregoing reasons, and respectfully request that the present rejection be reversed.

C. The Cited References "Teach Away" from Appellants' Claimed Invention

It is the Examiner's position that obtaining or utilizing a pure form of any pharmaceutical agent would be obvious to the skilled artisan because of the desire to reduce any adverse effect caused by the contaminant. Appellants respectfully assert that the Examiner's position cannot constitute a proper basis for a rejection under 35 U.S.C. § 103(a), *when the cited art describes these steroid impurities as desirable or as producing no adverse effects*. Therefore, *none* of the cited references provides any motivation for removing these steroidal impurities.

U.S. Patent No. 5,504,074 to D'Amato et al.

Table 1 (col. 8) of the D'Amato patent discloses that estradiol (IC_{50} = 30.0 μM) exhibits the same, desired inhibitory effect on tubulin polymerization as 2-methoxyestradiol (IC_{50} = 1.9 μM), while estrone (IC_{50} > 40 μM) and 4-methoxyestradiol (IC_{50} > 40 μM) exhibit no observed activity within the experimental limits. Thus, the D'Amato patent teaches away from Appellants' invention of removing estradiol from a 2-methoxyestradiol composition, and *at best*, suggests that the presence of estrone and 4-methoxyestradiol would impart no effect (other than a

simple *dilution* effect) on the activity of the desired compound in a pharmaceutical composition. Nowhere in D'Amato is there any indication that estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 4-methoxyestradiol, or estrone have estrogenic or carcinogenic effects which counteract the effect of 2-methoxyestradiol.

U.S. Patent No. 5,521,168 to Clark.

The structures of preferred estrogen metabolites useful for lowering and controlling intraocular pressure (col. 2, lines 1-21) disclosed in Clark include estradiol, estrone, 2-hydroxyestradiol, 4-hydroxyestradiol, and 4-methoxyestradiol, each of which the Appellants seek to remove from their claimed composition. Further, Clark indicates that the "[m]ost preferred compounds include...2-hydroxyestradiol [and] 4-methoxyestradiol...." (col. 2. lines 22-55). Thus, Clark teaches away from Appellants' invention of *removing* estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 4-methoxyestradiol, and estrone from a 2-methoxyestradiol composition. Nowhere in Clark is there any indication that estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 4-methoxyestradiol, or estrone have estrogenic or carcinogenic effects which counteract the effect of 2-methoxyestradiol.

U.S. Patent No. 5,643,900 to Fotsis et al.

The Fotsis et al. patent (Table, col. 3-4; col. 3, lines 31-59) discloses that 4-methoxyestradiol (IC_{50} = 7.24 μM), 2-hydroxyestradiol (IC_{50} = 15.7 μM), estrone (IC_{50} = 26 μM), and estradiol (IC_{50} = 34.5 μM) exhibits the same desired effect on bFGF-induced proliferation of low density bovine capillary endothelial cells (BBCE) *in vitro* as 2-methoxyestradiol. Thus, the Fotsis et al. patent teaches away from Appellants' invention of removing 4-methoxyestradiol, 2-hydroxyestradiol, estrone, and estradiol from a 2-methoxyestradiol composition. Nowhere in Fotsis et al. is there any indication that estradiol,

2-hydroxyestradiol, 4-hydroxyestradiol, 4-methoxyestradiol, or estrone have estrogenic or carcinogenic effects which counteract the effect of 2-methoxyestradiol.

U.S. Patent No. 6,200,966 to Stewart et al.

The Stewart et al. patent specifically discloses (col. 6, lines 26-32) that "[f]or the purposes of this specification, the terms 'steroid', 'steroid analogue' or 'steroid-like' are to be understood to encompass 2-methoxyestradiol, 2-hydroxyestradiol, 2-methoxyestradiol-3[-]methyl ether, 4-methoxyestradiol and other compounds based around a steroid nucleus that have the relevant biological activities to be used for the purposes of the present invention." Thus, Stewart et al. teaches away from Appellants' invention of removing 2-hydroxyestradiol and 4-methoxyestradiol from a 2-methoxyestradiol composition. Nowhere in *Stewart* is there any indication that estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 4-methoxyestradiol, or estrone have estrogenic or carcinogenic effects which counteract the effect of 2-methoxyestradiol.

Appellants respectfully maintain that the Examiner's basis for rejection of Claims 1-13 and 21-25 under 35 U.S.C. § 103(a) is improper because one skilled in the art would not be motivated to remove these steroidal compounds. None of the D'Amato et al., Clark, Fotsis et al., or Stewart et al. patents provides any indication that common steroidal impurites such as estradiol, 2-hydroxyestradiol, 4-hydroxyestradiol, 4-methoxyestradiol, and estrone have estrogenic or carcinogenic effects which counteract the effect of 2-methoxyestradiol. These steroidal contaminants are described as *desirable* in the cited references, or at worst, as producing no adverse effects, therefore D'Amato et al., Clark, Fotsis et al., and Stewart et al. all teach away from removing steroid contaminants in 2-methoxyestradiol pharmaceutical compositions.

Accordingly, Appellants respectfully maintain that none of Claims 1-13 and 21-25 is rendered obvious by D'Amato et al., Clark, Fotsis et al., or Stewart et al. under 35 U.S.C. §

103(a), and respectfully request that the final rejection be withdrawn and these claims be allowed.

D. The 2-Methoxyestradiol Composition of Stewart et al. Is Not Obtainable in High Purity

The final rejection states that Claims 1-13 and 21-25 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Stewart et al. on the basis of the commercially available 2-methoxyestradiol sample obtained from Sigma and used in Stewart et al. It is the Examiner's position that the Sigma Certificate of Analysis discloses the claimed compound can be obtained with a minimum 98% purity, which implies that the compound is *obtainable* in 98-100% purity as determined by HPLC using Sigma's method. Appellants respectfully submit that the Examiner has improperly interpreted this reference.

The Sigma Certificate of Analysis filed as Exhibit A (in the Appellants' Response filed December 14, 2001) shows the 2-methoxyestradiol sold by Sigma Chemical Company can be reproducibly obtained in at least 98.0% purity as determined by HPLC, and indicated in the "Specification" column of the Certificate. This 2-methoxyestradiol sample sold by the Sigma (Lot No. 83H4065 used in *Stewart*) in fact analyzed with a purity of exactly 98.0% as determined by HPLC (See *"Results"* column of Exhibit A for the actual HPLC purity of 98.0%). The Office Action of August 9, 2002 incorrectly states that the compound utilized in *Stewart* is "obtainable" or "can be obtained" at 100% purity. *The Sigma Certificate of Analysis supports no such conclusion.* Rather, the Certificate of Analysis merely states a lower limit of purity, *not* an obtainable upper limit of purity. Appellants respectfully note that the only inference that can be drawn from this Certificate of Analysis is that 2-methoxyestradiol *cannot* reproducibly be obtained any more pure than the minimum stated Specification of 98%.

Thus, the Sigma Certificate of Analysis *only* supports the fact that up to 2% contamination or impurities is an acceptable level in the commercial 2-methoxyestradiol sold by

Sigma. Lot No. 83H4065 used in Stewart et al. (col. 10, lines 13-17) in fact contains the highest level of 2% contamination. Nothing in Stewart et al. or in this Certificate of Analysis supports the notion that a 100% pure product is obtainable using Sigma's method.

Accordingly, Appellants respectfully maintain that none of Claims 1-13 and 21-25 is rendered obvious by Stewart et al. under 35 U.S.C. § 103(a), and respectfully request that the final rejection be reversed and these claims be allowed.

E. One of Ordinary Skill Would Expect Commercial 2-Methoxyestradiol to be Impure

The final rejection also states that Claims 1-13 and 21-25 are rejected under 35 U.S.C. § 103(a) over D'Amato et al., Clark, Fotsis et al., or Stewart et al., because it is the Examiner's position that the cited references do not show that the recited steroidal contaminants that Appellants seek to remove are actually present in the samples used in these patents. The Examiner states that the ordinary artisan would have the reasonable expectation that the compound is in pure form. Appellants respectfully disagree and show that one of ordinary skill would instead expect commercially available 2-methoxyestradiol to be impure.

As stated in the Response filed December 14, 2001, D'Amato et al., Clark, and Fotsis et al. are each completely silent with respect to 2-methoxyestradiol purity. None of these patents describes how the 2-methoxyestradiol was made nor provides any information as to the source of the 2-methoxyestradiol employed in the experiments described therein. Therefore, it may be fairly concluded that the source was commercial and it cannot be assumed that the 2-methoxyestradiol was pure. Indeed, Appellants have examined the purity of commercially available samples of 2-methoxyestradiol (see Table 1 of the Specification, page 18) and shown them to be contaminated with steroidal contaminants.

Further, Appellants respectfully note that synthetic methods for preparing most steroids utilize steroidal precursors, which are subsequently reacted to modify, add, or remove

various substituents while maintaining an intact steroid core, while providing the desired compound. As a result, steroidal impurities, notably estradiol, estrone, and various synthetic intermediates, are inherent in a sample of a target steroid such as 2-methoxyestradiol (Specification page 2, lines 8-15).

Accordingly, Appellants respectfully assert that none of Claims 1-13 and 21-25 is rendered obvious by D'Amato et al., Clark, Fotsis et al., or Stewart et al. under 35 U.S.C. § 103(a), and respectfully request that the final rejection be reversed and these claims be allowed.

F. Summary

For the foregoing reasons, the Examiner's rejections of Claims 1-13 and 21-25 were erroneous, and reversal of her decision is respectfully requested. The filing fee of $320, set forth in § 1.17(c), is included with this brief.

Respectfully submitted,

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